Supporting Information for the Letter Entitled

“N-Heterocyclic Carbene Catalyzed Trifluoromethylation of Carbonyl Compounds”

Jinhua J. Song,* Zhulin Tan, Jonathan T. Reeves, Fabrice Gallou, Nathan K. Yee and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Old Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877

Table of Contents

Experimental Procedures and Data for Compounds 6a-6n	S1-S11
Copies of ¹ H NMR Spectra for Compounds 6a-6n	S12-S25

General procedures: All reactions were performed in oven-dried glassware under nitrogen with magnetic stirring. All commercial reagents were used as received. Flash chromatography was performed using 230-400 mesh silica gel.

6a

To benzaldehyde (**5a**, 0.53 g, 5.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL), TMSCF₃ (2.0 g, 14.0 mmol), and carbene **1** (8.5 mg, 0.025 mmol). The mixture was stirred at room temperature for 45 min. HCl solution (2 N, 5 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (20 mLx3). Organic layers were combined and washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), dried over MgSO₄. Solvents

were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (30% ethyl acetate/hexanes) to give 0.65 g product **6a** (73% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (m, 2H), 7.41 (m, 3H), 5.03 (q, $J = 3.04$ Hz, 1H), 2.52 (d, $J = 4.04$ Hz, 1H).

6b

To **5b** (0.74 g, 5.6 mmol) in a dry flask under N_2 were added DMF (anhydrous, 6 mL) and TMSCF_3 (2.4 g, 16.9 mmol). After the mixture was cooled to $-25\text{ }^\circ\text{C}$, carbene **1** (9 mg, 0.028 mmol, 0.005 eq) was added. The mixture was warmed to room temperature and stirred at that temperature until **5b** was consumed as determined by HPLC (60 min). A 2 N HCl solution (6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO_3 aqueous solution (15 mL), brine (15 mL), and dried over MgSO_4 . Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.98 g product **6b** (87% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 7.72 (d, $J = 8.36$ Hz, 2H), 7.62 (d, $J = 8.44$ Hz, 2H), 5.12 (m, 1H), 3.12 (d, $J = 4.65$ Hz, 1H).

To **5c** (0.68 g, 4.8 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL) and TMSCF₃ (1.9 g, 13.5 mmol). After the mixture was cooled to -25 °C, carbene **1** (8 mg, 0.024 mmol, 0.005 eq) was added. The mixture was warmed to room temperature and stirred at that temperature until **5c** was consumed as determined by HPLC (60 min). A 2 N HCl solution (6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), and dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.88 g product **6c** (86% yield).

¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.38 (m, 4H), 5.04 (m, 1H), 2.65 (d, *J* = 3.28 Hz, 1H).

To 4-Methoxybenzaldehyde (**5d**, 0.61 mL, 5.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL), TMSCF₃ (2.1 g, 15 mmol), and carbene **1** (17 mg, 0.05 mmol). The mixture was stirred at room temperature until aldehyde was consumed as determined by HPLC (2 h 10 min). HCl solution (2 N, 6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water

(30 mL) was added and the aqueous layer was extracted with ether (20 mLx2). Organic layers were combined and washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (30% MTBE/hexanes) to give 0.835 g product **6d** (81% yield).

¹H NMR (CDCl₃, 400 MHz) δ 7.38 (d, *J* = 8.68 Hz, 2H), 6.92 (d, *J* = 8.80 Hz, 2H), 4.95 (m, 1H), 3.81 (s, 3H), 2.67 (d, *J* = 4.48 Hz, 1H).

To **5e** (0.60 g, 4.5 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL) and TMSCF₃ (1.9 g, 13.5 mmol). After the mixture was cooled to -25 °C, carbene **1** (7 mg, 0.021 mmol, 0.005 eq) was added. The mixture was warmed to room temperature and stirred at that temperature until **5e** was consumed as determined by HPLC (60 min). A 2 N HCl solution (6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), and dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.80 g product **6e** (89% yield).

¹H NMR (CDCl₃, 400 MHz) δ 7.42 -7.38 (m, 2H), 7.36-7.27 (m, 3H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 6.56, 16.0 Hz, 1H), 4.64 (m, 1H), 2.32 (brs, 1H).

6f

To 2,2-dimethyl-4-pentenal (**5f**, 1.36 mL, 10.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 10 mL), TMSCF₃ (4.2 g, 30 mmol), and carbene **1** (34 mg, 0.10 mmol). The mixture was stirred at room temperature for 4 h. HCl solution (2 N, 12 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (60 mL) was added and the aqueous layer was extracted with ether (40 mLx2). Organic layers were combined and washed with saturated NaHCO₃ aqueous solution (30 mL), brine (30 mL), dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% Et₂O/pentane) to give 1.29 g product **6f** (71% yield).

¹H NMR (CDCl₃, 400 MHz) δ 5.80 (m, 1H), 5.11 (d, *J* = 11.36 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 3.71 (q, *J* = 8.08 Hz, 1H), 2.45 (brs, 1H), 2.28 (dd, *J* = 8.08, 13.64 Hz, 1H), 2.05 (dd, *J* = 6.80, 13.60 Hz, 1H), 1.04 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz) δ 134.1, 125.8 (q, *J*_{C-F} = 282 Hz), 118.5, 75.2 (q, *J*_{C-F} = 28 Hz), 44.2, 36.7, 23.2, 22.8. HRMS was run using both APCI positive and negative with chloroacetonitrile and no molecular ion or major fragments were observed.

6g

To **5g** (0.52 g, 4.1 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL) and TMSCF₃ (1.7 g, 12.2 mmol). After the mixture was cooled to -25 °C, carbene **1** (7

mg, 0.021 mmol, 0.005 eq) was added. The mixture was warmed to room temperature and stirred at that temperature for 1 h. A 2N HCl solution (6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), and dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.73 g product **6g** (90% yield).

¹H NMR (CDCl₃, 400 MHz) δ 3.85-3.99 (m, 1H), 1.90-2.15 (brs, 1H), 1.51-1.80 (m, 2H), 1.20-1.50 (m, 10H), 0.91 (t, J = 8.00 Hz, 3H).

To hydrocinnamaldehyde (**5h**, 0.66 mL, 5.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL), TMSCF₃ (2.1 g, 15 mmol), and carbene 1 (17 mg, 0.05 mmol). The mixture was stirred at room temperature until aldehyde was consumed as determined by HPLC (3 h). HCl solution (2 N, 6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (20 mLx2). Organic layers were combined and washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (20% Et₂O/hexanes) to give 0.816 g product **6h** (80% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (m, 2H), 7.22 (m, 3H), 3.88 (m, 1H), 2.92 (m, 1H), 2.74 (m, 1H), 2.22 (d, J = 6.12 Hz, 1H), 2.05-1.85 (m, 2H).

To **5i** (0.63 g, 5.6 mmol) in a dry flask under N_2 were added DMF (anhydrous, 5 mL) and TMSCF_3 (2.4 g, 16.8 mmol). After the mixture was cooled to $-25\text{ }^\circ\text{C}$, carbene **1** (9 mg, 0.028 mmol, 0.005 eq) was added. The mixture was warmed to room temperature and stirred at that temperature for 1 h. A 2 N HCl solution (6 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO_3 aqueous solution (15 mL), brine (15 mL), and dried over MgSO_4 . Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.83 g product **6i** (81% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 3.72 (m, 1H), 2.05 (d, J = 6.64 Hz, 1H), 1.91 (d, J = 12.04 Hz, 1H), 1.84-1.63 (m, 5H), 1.33-1.10 (m, 5H).

To a DMF (anhydrous, 3.0 mL) solution of **5j** (0.150 g, 1.0 mmol) were added TMSCF_3 (0.74 mL, 5 mmol) and carbene **1** (3.4 mg, 0.01 mmol). The mixture was stirred at room temperature for 30 min. A 2 N HCl solution (6 mL) was added and the solution was

stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with dichloromethane (20 mL x 5). Solvents were removed under vacuum to give 185 mg of **6j** (84% yield).

^1H NMR (MeOH- d_4 , 400 MHz) δ 7.93 (d, J = 8.32 Hz, 2H), 7.49 (d, J = 8.08 Hz, 2H), 5.01 (q, J = 6.8 Hz, 1H).

To cyclohexyl pyruvate (**5k**, 0.860 g, 5.0 mmol) in a dry flask under N_2 were added DMF (anhydrous, 5 mL), TMSCF_3 (0.7 g, 5 mmol) and carbene **1** (17 mg, 0.05 mmol). The mixture was stirred at room temperature for 30 min. TBAF (5.5 mL, 5.5 mmol, 1 M/THF) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product (10 min). Water (30 mL) was added and the aqueous layer was extracted with ether (20 mLx2). Organic layers were combined and washed with saturated NaHCO_3 aqueous solution (15 mL), brine (15 mL), dried over MgSO_4 . Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (20% Et_2O /hexanes) to give 0.745 g product **6k** (62% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 4.97 (m, 1H), 3.89 (s, 1H), 1.85 (m, 2H), 1.73 (m, 2H), 1.58 (s, 3H), 1.56 (m, 3H), 1.42 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.8, 126.6 (q, $J_{\text{C-F}}$ = 284 Hz), 74.7 (q, $J_{\text{C-F}}$ = 30 Hz), 31.0, 30.8, 25.1, 23.1, 23.0, 19.0. HRMS (APCI negative with chloroacetonitrile): calc'd for $\text{C}_4\text{H}_4\text{O}_3\text{F}_3$ (loss of cyclohexyl), m/z 157.0112, obs'd m/z 157.0118.

To ethyl 4-phenyl-2-oxobutyrates (**5l**, 2.0 mL, 10.5 mmol) in a dry flask under N₂ were added DMF (anhydrous, 10.5 mL), TMSCF₃ (1.5 g, 10.5 mmol) and carbene **1** (37 mg, 0.11 mmol). The mixture was stirred at room temperature for 1 h. TBAF (11.6 mL, 11.6 mmol, 1 M/THF) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product (1.25 h). Water (60 mL) was added and the aqueous layer was extracted with ether (40 mLx2). Organic layers were combined and washed with saturated NaHCO₃ aqueous solution (30 mL), brine (30 mL), dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (5% EtOAc/hexanes) to give 1.57 g product **6l** (54% yield).

¹H NMR (CDCl₃, 400 MHz) δ 7.30 (m, 2H), 7.18 (m, 3H), 4.32 (m, 1H), 4.21 (m, 1H), 3.96 (s, 1H), 2.85 (m, 1H), 2.45 (m, 1H), 2.32 (m, 1H), 2.20 (m, 1H), 1.31 (t, *J* = 7.08 Hz, 3H).

To **5m** (0.83 g, 5.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 5 mL) and TMSCF₃ (2.1 g, 15 mmol). After the mixture was cooled to -25 °C, carbene **3^{8b}** (0.5 mmol) was added. The mixture was warmed to room temperature and stirred at that temperature for 1 h. A 2 N HCl solution (6 mL) was added and the solution was stirred at

room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ aqueous solution (15 mL), brine (15 mL), and dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by silica flash chromatography (10% to 30% ethyl acetate in hexanes) to give 0.88 g product **6m** (75% yield).

¹H NMR (CDCl₃, 500 MHz) δ 8.24 (d, J = 8.75 Hz, 2H), 7.79 (d, J = 8.55 Hz, 2H), 2.54 (brs, 1H), 1.83 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz) δ 151.2, 144.5, 126.8, 124.4 (q, J_{C-F} = 284 Hz), 122.7, 23.4. HRMS was run on the TMS protected product (APCI negative with chloroacetonitrile): calc'd for C₉H₈NO₃F₃Cl (loss of TMS, and chloride adduct), calc'd m/z 270.0144, obs'd m/z 270.0162.

To *p*-acetyl benzaldehyde (**5n**, 0.296 g, 2.0 mmol) in a dry flask under N₂ were added DMF (anhydrous, 6 mL), TMSCF₃ (1.5 mL, 10 mmol). Carbene **1** (3.4 mg, 0.01 mmol) was added. The mixture was stirred at room temperature for 30 min. NaOH aqueous solution (6 N, 3 mL) was added and the solution was stirred at room temperature until all TMS protected intermediate converted to product. The mixture was neutralized to pH 7 using HCl aqueous solution (6 N). The aqueous layer was extracted with MTBE (20 mLx2). Organic layers were combined and dried over MgSO₄. Solvents were removed under vacuum to give the crude residue, which was purified by flash chromatography (10% ethyl acetate/hexanes) to give 0.37 g product **6n** (85% yield).

^1H NMR (CDCl_3 , 400 MHz) δ 8.00 (d, $J = 6.80$ Hz, 2H), 7.60 (d, $J = 8.08$ Hz, 2H), 5.12 (m, 1H), 2.71 (d, $J = 4.56$ Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 198.3, 139.1, 137.7, 128.5, 128.2, 127.4, 126.4, 124.0 (q, $J_{\text{C-F}} = 281\text{Hz}$), 72.2 (q, $J_{\text{C-F}} = 32$ Hz), 26.7. HRMS (APCI positive): calc'd for $[\text{M}+1]^+$ $\text{C}_{10}\text{H}_{10}\text{O}_2\text{F}_3$, m/z 219.0627, obs'd m/z 219.0630.

CDCl₃ opt/xwinmr guest

7.26

107
3.75
3.73
3.73
3.72
3.71
3.70
2.06
2.04
1.92
1.89
1.82
1.81
1.80
1.78
1.78
1.77
1.72
1.70
1.67
1.59
1.32
1.31
1.29
1.29
1.26
1.25
1.25
1.23
1.22
1.20
1.20
1.18

CDCl₃, 400 MHz